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(54) Title: PROCESS FOR THE PREPARATION OF DENDRIMERS (57) Abstract <p>Process for the preparation of dendrimers wherein a starting compound successively in different reaction steps is reacted with a reactant in each of successive different steps, the reactant being different from one step to the next and the reactant being applied in excess in at least one of the steps, while in at least one of the steps the excess of the reactant is extracted with an extraction agent in a supercritical state. The extraction agent may also contain an entrainer.</p>		

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PROCESS FOR THE PREPARATION OF DENDRIMERS

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The invention relates to a process for the preparation of dendrimers wherein a starting compound successively in different reaction steps is reacted with a reactant, the reactant being different from one step to the next and the reactant being applied in excess in at least one of the steps.

From Angew. Chem. Int. Engl. 29 (1990), pp. 138-175, it is known to prepare dendrimers starting from the so-called 'excess-reactant method'. In such a process a nucleophilic core, such as for instance ammonia, is reacted in a Michael addition reaction with an excess of methyl acrylate, so that each ammonia molecule reacts with three molecules of methyl acrylate. After removal of the excess of methyl acrylate, the reaction product obtained is reacted with an excess of ethylene diamine in an amidation reaction. In order to suppress undesirable side reactions as much as possible, a molar excess of between 4:1 and 50:1 of ethylene diamine relative to methyl acrylate groups is supplied. After termination of the amidation reaction the excess of ethylene diamine is removed by means of vacuum distillation.

The process described in Angew. Chem. Int. Engl. 29 (1990), pp. 138-175 has the disadvantages that the customary methods for the isolation of the dendrimers and the separation of dendrimers from the reactants and/or solvent in order to avoid undesirable side reactions in subsequent reaction steps, are insufficiently efficient and take too much time, and that the amount of reactants and/or solvent in the remaining reaction mixture is reduced to an insufficiently low level.

In a publication in Science 251, 1991, pp. 1562-1564, it is mentioned that processes for the preparation of dendrimers on a commercially attractive scale still have to be developed.

In Mechanical Engineering, Aug. 1991, pp. 60-63, it is described that the preparation of dendrimers can only be carried out batchwise, on a small scale, in quantities varying from a few grammes up to, at most, a quarter of a pound. According to this publication, continuous processes for the preparation of dendrimers on a commercially attractive scale are not yet available.

It is the object of the present invention to provide an economically attractive process for the preparation of dendrimers, with which undesirable substances, such as for instance the excess of reactants and/or solvent, can be removed fast and simply, down to a low level, on a commercially attractive scale.

This is achieved according to the invention in that in at least one of the reaction steps the excess of the reactant is extracted with an extraction agent in a supercritical state.

Supercritical extraction as such has already been known for a long time and is applied to styrene polymers for instance in US-A-4703105. From US-A-4703105 it is known that residual solvent, oligomers, catalyst or volatile condensation products in styrene polymers can be reduced fast to a low level by contacting the styrene polymer in the molten or solid state with an extraction agent in or close to the supercritical state. Although such a supercritical extraction process has already been known for a long time, the elimination of the above-mentioned problems by application of supercritical extraction in the preparation of dendrimers on a commercial scale is nowhere suggested.

According to the invention, the supercritical state of an extraction agent is understood to mean the state in which the temperature is higher than or equal to 0.9 times the critical temperature and the pressure is higher than or equal to 0.9 times the critical pressure of the extraction agent.

The process according to the invention offers

the advantage that undesirable substances present in the reaction mixture can be removed fast and simply down to a low level and that the preparation of dendrimers can be carried out in an economical way on a commercially attractive scale.

According to the invention one extraction agent or a mixture of two or more extraction agents can be used. Application of a mixture of extraction agents offers the advantage that both the extraction capacity and the extraction selectivity can be further increased.

'Extraction capacity' according to the invention is understood to be the volume of a substance that can be extracted per volume unit of extraction agent. 'Extraction selectivity' according to the invention is understood to be the volume of a certain substance that is extracted relative to the total volume of extracted substances.

It has been found that, with the process according to the invention, the selectivity of successive reaction steps can be improved. Residual reactants or side products remaining in the reaction mixture may start acting as core molecules and give rise to the formation of undesired side products. As a result, for instance, dendrimers with a different core molecule may be formed, dendrimers with several different generations may be present simultaneously in the reaction mixture and dendrimers with structure defects may be formed.

It has also been found that with the process of the invention the purity of the dendrimer can be enhanced significantly.

According to the invention the extraction agents are mostly selected in such a way that the degradation temperature of the dendrimer is higher than 0.9 times the critical temperature of the extraction agent. In particular, the extraction agents according to the invention have a high affinity to the substances to be removed, for instance reactants and/or solvents.

Suitable extraction agents according to the

invention are for instance NH_3 , CO_2 , CO , NO , NO_2 , N_2O , N_2 , SO_2 , $\text{C}_1\text{-C}_5$ alkanes or alkenes, such as for instance methane, ethane, propane, pentane, ethene and propene, halogenated hydrocarbons having 1 or 2 carbon atoms, for instance dichloromethane, halogenated sulphur compounds for instance sulphur hexafluoride and ethers such as for instance dimethyl ether. According to the invention, ethane, ethene or CO_2 are preferably used as extraction agent. Such extraction agents offer the advantage of possessing a high extraction selectivity.

The extraction agent according to the invention will be selected depending on, among other things, the polarity of the substance to be extracted, the solubility of the substance to be extracted in the extraction agent, the selectivity of the extraction agent towards the substance to be extracted, and the thermal stability of the dendrimer. Mostly the supercritical extraction agent is selected so that it does not react with the substances to be extracted, nor with the dendrimer. For the extraction of polar substances, polar extraction agents may be used, while for the extraction of apolar substances, mostly apolar extraction agents will be used. In the process according to the invention, apolar extraction agents are mostly used.

According to the invention the supercritical extraction is mostly carried out at a reduced extraction temperature between 0.9 and 2. By 'reduced extraction temperature' in the framework of the invention is understood the ratio between the actual extraction temperature ($T(K)$) and the critical temperature ($T_c(K)$) of the extraction agent.

The supercritical extraction temperature applied according to the invention depends on, among other factors, the critical temperature of the extraction agent applied. The supercritical extraction temperature will mostly be chosen as high as possible in order to realize the highest possible volatility of the substance(s) to be

extracted. The extraction temperature applied also depends on other factors, for instance the thermal stability of the dendrimer and the substance to be extracted and the safety requirements in relation with the reaction conditions.*

According to the invention mostly a supercritical extraction temperature between 0 and 300°C is applied, in particular between 10 and 200°C, preferably between 20 and 150°C.

The process according to the invention is mostly carried out at a reduced pressure of between 0.9 and 10. By 'reduced pressure' according to the invention is understood the ratio between the absolute pressure applied and the critical pressure of the extraction agent. Optionally, other pressures may be applied, taking into account the extraction temperature and the safety requirements. In the process according to the invention the pressure is chosen in such a way that the separating effect and the extraction selectivity of the extraction agent are as high as possible.

In the process according to the invention, mostly a pressure between 10 and 1500 bar is applied, preferably between 50 and 800 bar, more preferably between 50 and 350 bar.

In the process according to the invention the extraction temperature and pressure are chosen in such a way that there is always a two-phase system present. Such a two-phase system comprises a first phase which contains the dendrimer, optionally still provided with the substances to be extracted, and a second phase which contains the extraction agent, optionally already provided with the substances to be extracted.

The mass ratio of the amount of extraction agent applied relative to the amount of dendrimer is mostly chosen between 1 and 1000. A frequently applied ratio according to the invention is between 1 and 500, preferably between 1 and 100. It has been found that with

such ratios the undesirable substances present in the dendrimer can be extracted to a residual content < 1 wt.%, often between 100 and 1 ppm or lower than 1 ppm, i.e. down to the detection limit of the substance concerned, even if
5 a 100-fold excess of the substance to be removed is present in the reaction mixture that is subjected to the supercritical extraction.

A suitable filling degree of the reactor used in the supercritical extraction according to the invention is
10 mostly between 10 and 80%. The reactor filling degree according to the invention is understood to mean the ratio of the volume occupied by the dendrimer to the reactor volume. With such a filling degree a suitable retention time and a good mass transfer can be realized, resulting
15 in a high extraction capacity and selectivity, within periods of time that are economically attractive for the process. Frequently applied filling degrees are between 20 and 75%. Such filling degrees offer the additional advantage that the extraction is well reproducible. If
20 lower filling ratios are applied, the retention time of the extraction agent in the dendrimer phase may become too short and result in a less good mass transfer during the supercritical extraction, as well as less good reproducibility of the supercritical extraction.

In the process according to the invention, it is
25 also possible to add so-called 'entrainers' to the extraction agent. The advantage of the addition of such entrainers is that the extraction selectivity towards polar contaminations can be enhanced considerably.
30 Suitable entrainers according to the invention are for instance water, alcohols, N₂O, ethene, ethers, for instance dimethyl ether and tetrahydrofuran, volatile low-molecular ketones for instance acetone and volatile low-molecular esters. According to the invention an alcohol,
35 more preferably methanol, is used as entrainer. The entrainers used according to the invention in particular may be substances that are applied in a possible

subsequent reaction step in the process for the preparation of the dendrimers. The use of these particular entrainers offers the advantage that there is no need to remove these entrainers in a separate purification step.

5 The extraction temperature is mostly chosen in such a way that the entrainer does not react or reacts as little as possible, for instance with the substances to be extracted and/or the dendrimer.

10 The amount of entrainers applied is mostly 2-30 wt.%, preferably 5-15 wt.%, relative to the weight of extraction agent applied.

 The supercritical extraction according to the invention may be carried out batchwise as well as continuously.

15 Dendrimers according to the invention are understood to be dendrimers as described in Angew. Chem. Int. Engl. 29 (1990) pp. 138-175, WO-A-9314147, WO-A-9502008, EP-A-115771, US-A-5041516, WO-A-9214543, US-A-4410668 and US-A-4289872.

20 According to the invention the starting compound preferably is a core molecule. Suitable core molecules may be chosen for instance from the group comprising ammonia, water, methanol, polymethylene diamines, for instance hexamethylene diamine, ethylene diamine, 1,4-diamino-
25 butane, polyalkylene polyamines, for instance diethylene - triamine, triethylene tetramine, tetraethylene pentamine, linear and branched polyethylene imines, primary amines, for instance methyl amine, hydroxyethyl amine, octadecyl amine, polyamino alkylarenes, for instance
30 1,3,5-tris(aminomethyl)benzene, tris(aminoalkyl)amines, for instance tris(aminoethyl)amine, heterocyclic amines, for instance imidazolines and piperidines, other amines for instance hydroxyethyl aminoethyl amine, mercaptoethyl amine, morpholine, piperazine, pentaerythritol,
35 polyalkylene polyols, for instance polyethylene glycol and polypropylene glycol, glycols, for instance ethylene glycol, polyalkylene polymercaptans, 1,2-dimercaptoethane,

phosphine, ϵ -aminocaproic acid, glycine, thiophenols, phenols, melamine and derivatives thereof, for instance melamine tris(hexamethylene diamine). Preferably, in the process according to the invention a core is used that is
5 chosen from the group comprising ammonia, polymethylene diamines, glycols and tris(1,3,5-aminomethyl)benzene. More preferably, ammonia or 1,4-diaminobutane is applied as core molecule.

Other suitable core molecules according to the
10 invention are for example (co)polymers containing one or more functional groups for example an amine, alcohol or thiol group. Examples of such (co)polymers are styrene-maleimide copolymers, styrene-acrylonitrile copolymers, vinyl formamide copolymers, polyethylene imines and
15 polymers, for instance polypropylene oxide, polystyrene and ethene-propene-diene copolymers that have been functionalized with one or more of the above-mentioned functional groups, for instance NH_2 groups.

Other suitable core molecules according to the
20 invention are for example low-generation dendrimers, for instance dendrimers of the 1st, 2nd and/or 3rd generation, as described in US-A-4507466 and F. Vögtle et al., Synthesis, February 1978, pp. 155-158.

The reactant according to the invention is
25 mostly chosen from the series of saturated and unsaturated nitriles, halogen cyanides with 3-50 carbon atoms which contain one or more cyanide groups -for instance mono- and polycyanides of n-propyl chloride, n-butyl chloride, isobutyl chloride, hexyl chloride, heptyl chloride, n-
30 propyl bromide, isobutyl bromide, hexyl bromide, heptyl bromide- α,β -ethylenically unsaturated amides or esters, polyols, ethylenically unsaturated sulphides, alkylene polyamides and polyalkene polyamines, for instance ethylene diamine, diethylene triamine, triethylene
35 tetramine, α,β -ethylenically unsaturated esters, acids and nitriles containing an acrylyl group, for instance methyl acrylate, ethyl acrylate, acrylonitrile, methyl itaconate,

dimethyl fumarate, maleic anhydride, acrylamide, vinyl cyanides that correspond to formula 1:



- 10 where A = $-\overset{\overset{O}{\parallel}}{C} = N$, $-\overset{\overset{O}{\parallel}}{C} - \overset{\overset{H}{\mid}}{N} - R^3$, $\overset{\overset{O}{\parallel}}{C} - O - R^3$, or $\overset{\overset{O}{\parallel}}{C} - R^3$
 $R^1 = -H$ or $-CH_3$,
 $R^2 = -H$, $-CH_3$, or a hydrocarbon compound with 2-
 18 carbon atoms which contains at least one
 15 double bond, conjugated with the double
 bond of formula 1, for instance
 $-CH = CH_2$ and $-CH = C - CH = CH_2$,
 $R^3 =$ a hydrocarbon compound with 1-18 carbon
 atoms which contains 1-5 cyanide groups.

The reactant according to the invention
 20 preferably belongs to the group of acrylonitrile,
 methacrylate and ethylene diamine.

The process according to the invention is very
 well suited for the removal of a large number of solvents
 and reactants down to a low level. Examples of solvents
 25 and/or reactants that can be removed with the process
 according to the invention are, inter alia, acid
 anhydrides for example maleic anhydride; esters, for
 instance C_1 - C_4 alkylesters of various polycarboxylic acids,
 for instance benzene tricarboxylic acid, acrylic acid and
 30 methacrylic acid and the corresponding acrylate and
 methacrylate esters of which the alkyl group contains 1 to
 4 carbon atoms, for instance methyl acrylate, ethyl
 acrylate, methyl methacrylate, methyl itaconate; vinyl
 cyanides that correspond to formula 1, for instance
 35 acrylonitrile, methacrylonitrile, ethacrylonitrile;
 halogen cyanides with 3-50 carbon atoms which contain one
 or more cyanide groups, for instance mono- and
 polycyanides of n-propyl chloride, n-butyl chloride,
 isobutyl chloride, hexyl chloride, heptyl chloride, n-

propyl bromide, isobutyl bromide, hexyl bromide, heptyl bromide; aliphatic and aromatic mono- and polyamines; alkylene polyamines and polyalkylene polyamines, for instance ethylene diamine, 1,4-diaminobutane, 1,6-hexamethylene diamine, diethylene triamine, benzyl amines for instance tris(1,3,5-aminomethyl)benzene; alkanol amines such as ethanol amine; aziridines and derivatives thereof, for instance N-aminoethyl aziridine; sulphur compounds for instance polythiols, for instance $C(CH_2SH)_4$; sulphides for instance epichlorosulphide, ethylene sulphide; thiophenols; halogens; aromatic hydrocarbons, with or without substituents, for instance phenol and amides, for instance acrylamide.

The process according to the invention is particularly suitable for the preparation of dendrimers as described in WO-A-9314147 and WO-A-9502008. To this end according to the invention an amount of a core molecule, for instance 1,4-diaminobutane, is dissolved in methanol, and reacted with an excess of a vinyl cyanide, for instance acrylonitrile, in a Michael addition reaction whereby a nitrile-terminated reaction product is obtained. To minimize undesirable side reactions in subsequent reaction steps, the excess acrylonitrile is removed down to ppm level through a supercritical extraction with CO_2 as extraction agent. In a next reaction step, the nitrile groups of the resulting reaction product are hydrogenated in the presence of hydrogen whereby an amine terminated reaction product is obtained whereby water is used as a solvent. Thereafter, the amine terminated reaction product is again reacted with an excess of acrylonitrile. The Michael addition reaction and the hydrogenation reaction are repeated until a dendrimer of the desired generation is obtained. Optionally, the supercritical extraction procedure can be repeated a number of times, for example after every Michael addition reaction in case dendrimers of higher generations are prepared.

The process according to the invention is also

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suitable for the preparation of polyamidoamine dendrimers as described in Angew. Chem. Int. Engl. 29 (1990) pp. 138-175. In the process described in Angew. Chem. Int. Engl. 29 (1990) pp. 138-175, the following reaction steps are repeated alternately until a dendrimer of the desired generation or the desired molecular weight is obtained: for instance an amount of ammonia is reacted in a Michael reaction with an excess of methacrylate in methanol as solvent, so that every ammonia molecule reacts with three molecules of methylacrylate whereby an ester terminated reaction product is obtained. According to the invention the excess of methylacrylate is removed from the reaction mixture down to ppm level, for instance by means of a supercritical extraction whereby CO₂ is used as extraction agent. The resulting ester terminated reaction product is subsequently reacted in an amidation reaction with an excess of ethylene diamine, whereby methanol is used as solvent and whereby an amine terminated reaction product is obtained. The molar excess of ethylene diamine relative to methacrylate groups is between 4:1 and 50:1. According to the invention, upon termination of the amidation reaction, the excess of ethylene diamine is removed from the reaction mixture for instance by means of a supercritical extraction in an apolar extraction agent, for instance ethane to which 5 wt.% of methanol is added as entrainer. For the preparation of dendrimers of higher generations, the Michael reaction, the amidation reaction and the intermediate supercritical extractions may be repeated the required number of times.

The invention will be further elucidated in the following examples, without however being restricted thereto.

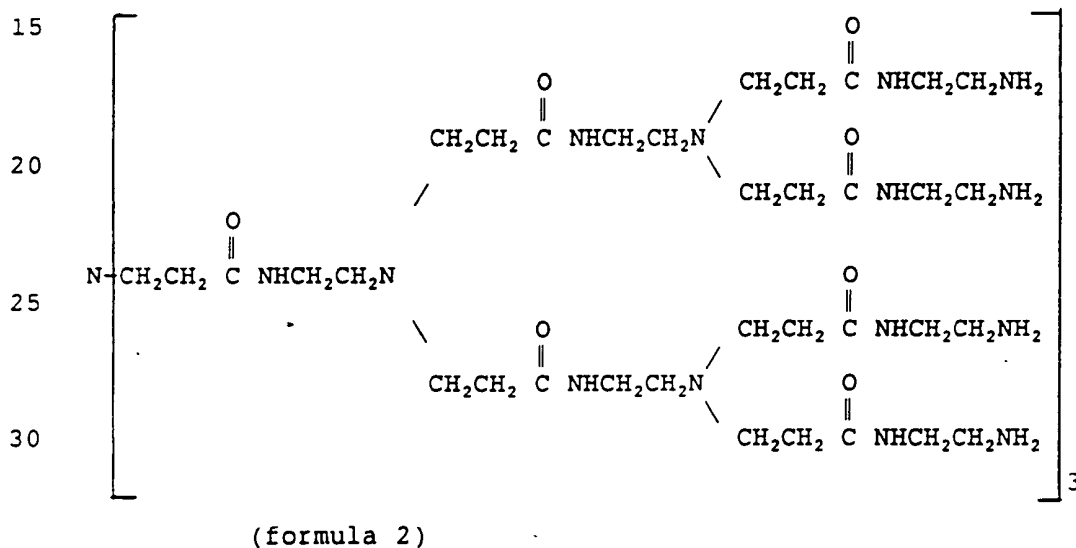
Example I

To an autoclave with a volume of 50 cm³ 20 g of a second-generation polypropylamine dendrimer, 8-cascade:1,4-diaminobutane[4]:(1-azabutylidene)⁴:

azabutyliidene)⁴: propionitrile containing 1 wt.% of acrylonitrile, was added. To remove the acrylonitrile from the polypropylamine dendrimer, a supercritical extraction was carried out, by passing a flow of 400 g of CO₂ through the dendrimer for 45 minutes, at a pressure of 180 bar and a temperature of 313 K. The residual acrylonitrile content of the dendrimer, as determined by gas chromatography, was less than 0.01 wt.%.

10 Example II

To an autoclave with a volume of 5 cm³, 2 g of a third-generation polyamidoamine dendrimer according to formula 2, containing 5 wt.% ethylene diamine is added.



35 A supercritical extraction is carried out by
passing a flow of 100 g of ethane to which 5 wt.% methanol
is added through the dendrimer phase for 60 minutes, at a
pressure of 180 bar and a temperature of 333 K. The
residual ethylene diamine content of the dendrimer
40 determined by gas chromatography is < 0.05 wt.%.

40 determined by gas chromatography is < 0.05 wt.%.

C L A I M S

1. Process for the preparation of dendrimers wherein a starting compound successively in different reaction steps is reacted with a reactant, the reactant being different from one step to the next and the reactant being applied in excess in at least one of the reaction steps, characterized in that in at least one of the reaction steps the excess of the reactant is extracted with an extraction agent in a supercritical state.
2. Process according to claim 1, characterized in that in at least two of the steps an excess of the reactant is applied.
3. Process according to any one of claims 1-2, characterized in that the supercritical extraction is carried out at a reduced extraction temperature between 0.9 and 2.
4. Process according to any one of claims 1-3, characterized in that a reduced extraction pressure between 0.9 and 10 is applied.
5. Process according to any one of claims 1-4, characterized in that the extraction agent is chosen from the series comprising CO₂, ethane and ethene.
6. Process according to any one of claims 1-5, characterized in that the extraction agent contains an entrainer.
7. Process according to claim 6, characterized in that the entrainer is an alcohol.
8. Process according to claim 7, characterized in that the entrainer is methanol.
9. Process according to claim 8, characterized in that the quantity of entrainer added amounts to 2-30 wt.% relative to the amount of extraction agent applied.
10. Process according to any one of claims 1-9, characterized in that the starting compound belongs to the series comprising ammonia, polymethylene

diamines, glycols and 1,3,5-tris(amino methylbenzene).

11. Process according to claim 10, characterized in that the starting compound is ammonia or 1,4-diaminobutane.
12. Process according to any one of claims 1-11 characterized in that the reactant belongs to the group consisting of α,β -ethylenically unsaturated nitriles which contain an acrylyl group, vinyl cyanides, alkylene polyamines and polyalkylene polyamines.
13. Process according to claim 12, characterized in that the reactant belongs to the series comprising acrylonitrile, methyl acrylate and ethylene diamine.
14. Process according to any one of claims 1-13, characterized in that the dendrimer is a polyamidoamine dendrimer or a polypropylamine dendrimer.
15. Process according to any one of claims 1-14, characterized in that
 - 1) 1,4-diaminobutane is reacted with an excess of acrylonitrile whereby a nitrile terminated reaction product is obtained, after which the excess of acrylonitrile is removed by means of a supercritical extraction with CO_2 ,
 - 2) the nitrile groups of the nitrile terminated reaction product are hydrogenated in the presence of hydrogen and in water as a solvent whereby an amine terminated reaction product is obtained,
 - 3) after which the amine terminated reaction product is reacted with an excess of acrylonitrile, whereby the excess of acrylonitrile is removed by means of a supercritical extraction with CO_2 ,whereby steps 2) and 3) are repeated alternately until a dendrimer of the desired generation is

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obtained.

16. Process for the preparation of a dendrimer according to any one of claims 1-14, characterized in that

- 5 1) ammonia is reacted with an excess of methyl acrylate whereby an ester terminated reaction product is obtained, after which the excess of methyl acrylate is removed by means of a supercritical extraction with CO₂,
 - 10 2) the ester terminated reaction product is reacted with an excess of ethylene diamine whereby an amine terminated reaction product is obtained and subsequently the excess of ethylene diamine is removed by means of a supercritical extraction with ethane to which 5 wt.% of
 - 15 3) the amine terminated reaction product is reacted with an excess of methyl acrylate, whereby an ester terminated reaction product is obtained, after which the excess of methyl acrylate is
 - 20 removed by means of a supercritical extraction with CO₂,
- whereby steps 2) and 3) are repeated alternately until a dendrimer of the desired generation is obtained.

INTERNATIONAL SEARCH REPORT

Intern. Application No PCT/NL 95/00249		
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C08G85/00 C08G73/02 B01D11/02 C07C253/34 C07C255/24		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C08G		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
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C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 14 no. 37 (C-680) ,24 January 1990 & JP,A,01 272601 (ASAHI DENKA KOGYO K K) 31 October 1989, see abstract <div style="text-align: center;">-----</div>	
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Date of the actual completion of the international search <div style="text-align: center;">21 August 1995</div>		Date of mailing of the international search report <div style="text-align: center;">08.09.95</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2220 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Stienon, P</div>

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